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BY HAND DELIVERY

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 98 N-0222, Dissemination of Information on Unapproved/New Uses for Marketed Drug, Biologics, and Devices, 63 Fed. Reg. 31143 (June 8, 1998)

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) respectfully submits these comments to the above-referenced docket. BIO appreciates the opportunity to provide input on these important new regulations implementing section 401, Dissemination of Information on New Uses, of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"). 63 Fed. Reg. 31143 (June 8, 1998). As set forth in detail below, however, BIO has very serious concerns with the Food and Drug Administration's ("FDA's") proposed regulations. The goal of Congress was to allow, under balanced circumstances, the dissemination of information on new uses of approved drugs. BIO believes that, as proposed, the regulations totally thwart the clear intent of Congress and thus substantial changes, as suggested below, must

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be made to ensure that the final regulations reflect the language and the intent of the law.

BIO represents the emerging biotechnology industry in the United States with over 790 companies and affiliated organizations as members. BIO members are involved in the research and development of health care, agricultural and environmental biotechnology products. The majority of BIO members are involved in the development and marketing of new drugs and biologics. BIO, therefore, has a significant interest in the development of regulations regarding dissemination of information on new or off-label uses of new drugs and biologics that serve the best interests of public health.

1. Executive Summary

Section 401 represents a carefully crafted approach to permit the dissemination of scientific information to physicians, insurers and other health professionals on new uses 1/ of approved medical products without reducing the incentives to file a supplemental application confirming the safety and efficacy of such new uses. As ultimately approved by Congress, the program expires in 2006. In less than three and one half years from now, the Comptroller General must submit to Congress a report on the scientific issues raised by the subchapter in order that Congress may determine whether to extend the program beyond its expiration date. Unfortunately, should the regulations be adopted as proposed, it will be impossible for the Comptroller General to prepare a meaningful report, because insufficient

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1/ Throughout this document, we use the term “new use,” a term that was adopted by Congress in the statute. It is important to note, however, that such uses may be either truly new uses or uses that have been used appropriately by health care practitioners for some time.

information will be available on which to base the study -- for the simple reason that only a very limited amount of scientific information will be disseminated under the new law. This is because the proposed regulations pervert the law and the intent of Congress by narrowing the type of scientific information eligible for dissemination and placing inappropriate limits on the ability to gain a waiver of the law's requirement to submit a supplemental application for the off-label use.

The proposal is paternalistic and cumbersome; it totally destroys the statute's balance between the desirability of dissemination and the policy favoring submission of an NDA/BLA supplement. Indeed, in many ways the proposed regulations appear to be designed for the purpose of making the program unattractive or unavailable to manufacturers. Wholesale revisions are required to conform the regulations to the intent of Congress and to make section 401 workable.

As set forth concretely below, numerous changes to the proposed regulations are necessary to recalibrate the balance Congress put into the statute. They include, among others, significant changes to FDA's definitions of "new use" and "clinical investigation"; significant changes to FDA's criteria for exemptions from the requirement for the submission of a supplemental application; and significant changes to the process FDA has proposed to ensure that the sixty-day time period for a decision by the agency regarding whether an article may be disseminated is, in fact, sixty days and not an unlimited time period subject to FDA discretion.

II. Introduction

Section 401 of FDAMA, Dissemination of Information on New Uses, was intended to allow companies to disseminate useful medical information to health care

practitioners to allow them to provide more effective treatment for their patients. It was carefully crafted to balance the need to get new use information on product labels through the submission and approval of supplemental applications with the need to permit manufacturers to provide health care providers and others with critical information about new product uses. The House Report on FDAMA succinctly describes the intent of Congress:

> The principal policy considerations that underlie this provision are the facilitation of greater access to timely and accurate information by health care providers. Coupled with this goal is a recognition that the FDA has a responsibility to protect the public health.

H.R. Rep. 105-310 at 60 (1997).

Section 401 authorizes dissemination of peer reviewed journals and reference publications (such as textbooks) that contain information on the safety or effectiveness of the new or off-label use of approved drugs and devices. In order to ensure that the desired balance was maintained in section 401, Congress drafted detailed requirements for this program. Indeed, of the approximately 75 substantive provisions of FDAMA, section 401 is the longest and most detailed provision. This level of detail was included to ensure that the intent of Congress was clear. 2/

It is critical to understand that Congress considered this program to be about dissemination of appropriate scientific information and not about promotion of unapproved uses. Therefore, Congress established a system that was intended to rely

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2/ Section 401 requires that FDA finalize regulations implementing this provision by November 21, 1998. The provision becomes effective either on the date that final regulation takes effect, or if no regulations are finalized, on November 21, 1998.

on the independent medical experts of carefully defined peer-reviewed scientific or medical journals to determine the scientific validity of the articles eligible for dissemination under this provision. It neither considered this to be a program that would require FDA to re-review the published peer-reviewed articles in detail nor expected that FDA would set publication criteria for the nation's most prestigious scientific and medical journals. Rather, if the submitted article about a clinical investigation is fully labeled according to this provision, including the disclaimer that the use is not approved by FDA, and the manufacturer meets the requirements with regard to filing a supplemental application, then the manufacturer may disseminate the article unless FDA objects within sixty days. 3/ This time frame was considered fully adequate by Congress given the nature of the program devised by Congress, which relies heavily on the expertise of independent experts conducting peer review for select scientific or medical journals. Congress also gave FDA increased authority to require that additional information be disseminated with an article and extensive authority to promptly take corrective actions. Lastly, at the request of FDA, Congress included a seven-year sunset provision in the statute and ordered a study by the Comptroller General (General Accounting Office) to evaluate this new program.

On June 8, 1998, FDA published proposed regulations to implement section 401 of FDAMA. Instead of maintaining the careful balance established by Congress, FDA proposed rules that will only discourage the dissemination of new or off-

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3/ The use of a disclaimer is an important factor in balancing the competing interests. Information disseminated by a company without any disclaimer that the use has not been approved by FDA could mislead. However, when it is clearly disclosed that the agency has not yet approved a use, this simple disclaimer goes a long way towards providing the necessary balance within the context of this entire program.

label use information and render meaningless any study of the program over the next seven years. These regulations would impose conditions on the dissemination program far beyond those required by the statute. As demonstrated below, they also severely limit the ability of manufacturers to disseminate to physicians and other health care providers high quality medical journals on relevant studies and pervert the law's exception to the requirement to submit a supplemental application on the off-label use if it would be economically prohibitive or unethical to do so.

III. FDA's Proposed Regulations Would Impose Conditions that Exceed the Statutory Requirements, Thereby Impeding the Flow of Important Medical Information to Health Professionals

A. Contrary to the Statute, The Proposed Regulations Contain Substantial Limitations on the Types of Clinical Investigations to Which Scientific Articles and Reference Publications May Pertain (Proposed 21 C.F.R. § 99.3)

Section 401 of FDAMA authorizes dissemination of:

> a reprint or copy of an article, peer reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug . . . involved, which was published in a scientific or medical journal . . . which is about a clinical investigation with respect to the drug . . . and which would be considered to be scientifically sound by such experts.

21 U.S.C. § 360aaa-1(a)(1)(A).

We believe that, contrary to the clear intent of the statute, as currently proposed FDA's regulations would severely limit the types of articles that could be disseminated under this provision. As described in detail below, both the proposal's restrictions on the types of clinical trials that may be the subject of a disseminated

article and the types and amount of information about the trials that such articles must include, provide significantly less flexibility than Congress envisioned. By issuing a proposal that would enable the agency to substitute its own judgment for that of the independent scientific experts (who are the peer reviewers identified in section 401) in determining whether a study is scientifically sound, FDA has utterly failed to implement the dissemination provisions in an appropriate manner.

1. Definition of "New Use"
(Proposed 21 C.F.R. § 99.3(g))

Section 401 provides that "information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling of a drug or device" may be disseminated "if the manufacturer meets the requirements of subsection (b)." 21 U.S.C. § 360aaa(a). While FDA incorporates this standard into its proposed definition of "new use," the preamble discussion regarding this standard indicates that the definition is so broad that it threatens to include information on approved uses. See proposed 21 C.F.R. § 99.3(g), 63 Fed. Reg. at 31145. In the preamble the agency states that, under the regulations, new uses would include, but not be limited to: completely different indications, modifications of an existing indications to include a new dose, new dosing schedules, new routes of administration, different durations of usage, new age groups, other patient subgroups, different stages of the disease, different intended outcomes (e.g., improved quality of life), effectiveness for a sign or symptom of the disease not in the current labeling, and comparative claims to other agents. 63 Fed. Reg. at 31145.

This proposed definition, as elaborated upon in the preamble, is entirely too broad. For example, certain comparative claims for approved indications may not

reflect a "new use" of the drug. Similarly, if a drug's approved labeling contains an indication that does not include a patient age limitation, statements describing the use of the drug in a certain age population should not be considered a new use unless the manufacturer makes claims for unique safety or efficacy in that group. The final regulation should narrow the scope of "new use" and, among other changes, clarify that under section 401, claims that are otherwise permitted, including certain comparative claims and those pertaining to subpopulations, will not be considered "new use" claims subject to the requirements of the statute.

2. Restrictions on the Types of Studies
(Proposed 21 C.F.R. § 99.3)

FDA's proposed regulations define a clinical investigation as "an investigation in humans that is prospectively planned to test a specific clinical hypothesis." Proposed 21 C.F.R. § 99.3(b), This definition, which restricts clinical investigations to those that are prospectively planned, is not part of the statute. Indeed, Congress provided enough detail in the statute that "clinical investigation" should not be defined at all by the agency. Congress established statutory criteria to determine whether an article about a clinical investigation is eligible for dissemination, thereby making further agency elaboration on this issue inappropriate.

Indeed, where, as here, the statute is unambiguous, FDA must effectuate Congress' intent. If a statute is clear on its face, the agency must give effect to Congress' intent. Immigration and Naturalization Service v. Cardoza-Fonseca, 480 U.S. 421,446-48 (1987). See also National Assoc. for Better Broadcasting v. FCC, 830 F.2d 270, 275 (D.C. Cir. 1987) (agency must give effect to the clear intent of Congress and if intent is clear "that is the end of the matter"); Overseas Educ. Assoc. Inc. v.

FLRA, 876 F.2d 960, 964 (D.C. Cir. 1989) (if the meaning of the statute is clear, both the court and the agency must give effect to the "unambiguously expressed intent of Congress").

In this instance, the intent of Congress is clear. First, Congress established that, in order to be eligible for dissemination, an article must be in the form of an unabridged:

> reprint or copy of an article, peer-reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved, which was published in a scientific or medical journal . . . which is about a clinical investigation with respect to the drug or device, and which would be considered to be scientifically sound by such experts.

21 U.S.C. § 360aaa-1(a)(1). Second, Congress defined the term "scientific or medical journal" as

> a scientific or medical publication (A) that is published by an organization (i) that has an editorial board; (ii) that utilizes experts, who have demonstrated expertise in the subject of an article under review by the organization and who are independent of the organization, to review and objectively select, reject, or provide comments about proposed articles; and (iii) that has a publicly stated policy, to which the organization adheres, of full disclosures of any conflict of interest or biases for all authors or contributors involved with the journal or organization; (B) whose articles are peer-reviewed and published in accordance with the regular peer-review procedures of the organization; (C) that is generally recognized to be of national scope and reputation; (D) that is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and (E) that is not in the form of a special supplement that has been funded in whole or in part by one or more manufacturers.

21 U.S. C. § 360aaa-5(5). Accordingly, Congress has already determined the criteria an article must meet in order to be eligible for dissemination. FDA inappropriately attempts to narrow this universe of articles by restricting it to those that are prospectively designed.

Such a restriction precludes the use of retrospective studies, which may provide important information, especially in situations where a new use has evolved into standard practice. This definition also would eliminate the use of studies that report case series. FDA simply lacks any authority to establish regulations that contradict the statute in this manner. See Immigration and Naturalization Service v. Cardoza-Fonseca, 480 U.S. at 446-48.

Moreover, even if the agency had the authority to narrow the universe of articles eligible for dissemination, the agency's proposed definition of "clinical investigations" would prohibit the dissemination of many types of important medical and scientific articles. Congress never expressed an intent to limit the types of information that could be disseminated in this manner and it is wholly inappropriate for FDA to adopt such restrictions, Section 552 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") states that an article must be "about a clinical investigation" and be published in a peer reviewed medical or scientific journal meeting the standards of section 556(5). By unreasonably restricting the definition of a clinical investigation, FDA causes us to question whether the agency truly is attempting to faithfully implement the law. Accordingly, the agency's proposed definition of "clinical investigation" should be deleted from the final rule.

3. FDA's Additional Requirements Regarding the Type and Amount of Information the Article Must Include to Qualify for Dissemination Interfere With the Peer-Review Process (Proposed 21 C.F.R. § 99.10 l(b)(l), 63 Fed. Reg. at 31146-47)

The language of FDAMA and its statutory history express Congress' decision to rely on the peer-review publication process to determine the "scientific soundness" of clinical investigations for purposes of the dissemination provision- See 21 U.S.C. § 360aaa-1 (a)(l). This process is conducted by the experts chosen by the journal that meet the criteria of section 556(5). FDA's proposed regulation would circumvent congressional intent by improperly allowing FDA to revisit such determinations:

> The determination of whether a clinical investigation is considered to be "scientifically sound" will rest on whether the design, conduct, data, and analysis of the investigation described or discussed in a reprint or copy of an article or in a reference publication reasonably support the conclusions reached by the authors.

Proposed 21 C.F.R. § 99.10 l(b)(l).

FDA has no authority under the statute to substitute its judgment for that of the expert peer-reviewers as it attempts to do through its proposed implementing regulations. The proposed regulations denigrate the function of peer-review. Had Congress intended for FDA to conduct the primary review of materials for purposes of the dissemination provision, Congress would have neither restricted eligible articles to those that have been "peer-reviewed and published in accordance with the regular peer review procedures of the organization" nor required that the journal be "generally

recognized to be of national scope and reputation. " See 21 U.S. C. § 360aaa-5(5). Further, by limiting the information that may be disseminated to peer-reviewed articles "about a clinical investigation with respect to the drug or device, and which would be considered to be scientifically sound *by such* experts, " Congress specifically provided that the determination regarding the scientific soundness was to be made by the journal peer-reviewers. Accordingly, FDA lacks any authority to issue regulations to the contrary. Chevron U. S. A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 842-43 (1 984).

In Chevron the Supreme Court developed a two-step inquiry. The first question is whether "Congress has directly spoken to the precise question at issue." Id. if intent is clear, the agency must give effect to the statute and issue regulations fully consistent with it as well. See NLRB v. United Food and Commercial Workers Union, 484 U.S. 112, 123 (1987). If the statute is silent or ambiguous, then the question is whether the regulations are based on a reasonable interpretation of the statute. See Chevron, 467 U.S. at 842. See also, Cardoza-Fonseca, 480 U.S. at 447-48; Coalition of NYS Career Schools v. Riley, 129 F.3d 276, 279 (2d Cir. 1997); NRDC v. EPA, 859 F.2d 156, 168-69 (D.C. Cir. 1988), Even then, the agency's regulations are entitled to deference only as long as the interpretation is consistent with the statute. See City of Boston v. HUD, 898 F.2d 828, 831 (1st Cir. 1990). In the case at hand, FDA's proposed interpretation of the statute is contrary to the language and intent of Congress and, therefore, must be amended.

The extent to which the agency is seeking to extend its own authority in this area is highlighted by the eight specific requirements set forth in the preamble to the proposed rule. See 63 Fed. Reg. 31143, 31146-7. The list of eight criteria

exemplifies FDA's effort at "piling on" requirements in an attempt to discourage dissemination of new use information. FDA states that it intends to use these criteria to judge whether a clinical investigation is "scientifically sound." Id. FDA's conclusion that the eight criteria cited in the preamble are necessary to "provide a basis for determining whether the conclusions [of the authors] are reasonably supported and the findings represent evidence of safety and effectiveness of the new use" demonstrate the agency's clear intent to ignore the fact that Congress already has decided that such determinations should rest in the hands of the scientific experts responsible for peer review. 63 Fed. Reg. at 31146.

FDA should not interfere with the peer-review process by imposing additional requirements on clinical trials to qualify for dissemination, some of which may not be consistent with certain current journal standards. Indeed, it appears that, through this back door route, FDA is attempting to regulate the standards and content of all journals by establishing these criteria. FDA has no place second-guessing the editorial boards and peer-reviewers of scientific and medical journals.

FDA should make clear in the final version of 21 C.F.R. § 99.10 l(b)(l) that the statutory criteria, and only the statutory criteria, apply. FDA should clarify that in order to be eligible for dissemination, an article must be about a clinical investigation and be published in a medical or scientific journal that meets the statutory criteria. The regulation, any preamble discussion, or future guidances should not add criteria that restrict the types of journals beyond what Congress provided. To that end, FDA should delete its proposed definition of "scientifically sound" and explicitly reject the eight criteria described in the preamble to the proposal rule.

B. FDA's Proposed Regulations Completely Undermine the Intent of Congress by Effectively Prohibiting the Distribution of Reference Publications (Proposed 21 C.F.R. $$99.101, 99.103)

The law requires FDA to permit the distribution of reference publications, including reference texts that meet the requirements of the statute. 21 U.S.C. § 360aaa-1 (b). In order to be disseminated, reference texts must not: (1) have been written, edited, excerpted, or published for or at the request of the manufacturer, (2) have been edited or "significantly influenced" by the manufacturer, (3) be solely distributed through such a manufacturer, (4) focus on any particular drug or device of the disseminating manufacturer, or (5) be false or misleading. Id. Instead of implementing the law Congress has written, FDA deliberately attempts to undermine the intent of Congress by proposing regulations that effectively prohibit the distribution of reference texts.

FDA's discussion of the issue in the preamble implies that it is Congress' statute, not the agency's regulations, that effectively prohibits the dissemination of reference texts. This is highly misleading. The statute makes it clear that FDA must allow the dissemination of reference texts that meet the requirements of the statute. In its proposed regulations, FDA narrowly limits the content of a reference text appropriate for dissemination. Ultimately, it is FDA's narrow definition --@ the statute -- that would limit the use of reference texts. The agency's states that, "FDA recognizes that the majority of such [reference texts] would probably not meet the requirements of section 401 of FDAMA and this proposed implementing regulation." 63 Fed. Reg. at 31146. Again, many reference texts may well meet the requirements of FDAMA, it is FDA's regulations and its unnecessary hurdles that will impede the dissemination of reference texts.

The agency cannot finalize the regulations as written, thereby failing to implement the statutory provisions with regard to reference texts. An agency cannot interpret language of a statute contrary to its plain language. See American Federation of Gov't Employees v. FLRA, 750 F.2d 143, 146 (D.C. Cir. 1984) (stating that an agency's interpretation cannot be contrary to the statutory mandate); see also, Baylor Univ. Med. Center v. Heckler, 758 F.2d 1052, 1062 (5th Cir. 1985). An agency interpretation must be "rational and consistent with the statute." See City of Boston, 898 F.2d at 831. Therefore, an agency interpretation is not entitled to deference if it is contrary to the plain language of the statute.

Moreover, the "solution" the agency proposes is to issue a guidance document to address this issue. This is not an option under the statute. FDAMA requires that the agency issue regulations to implement the law or, in the absence of regulations, the law will become effective November 21, 1998. 21 U.S. C. § 360aaa-6(d). Therefore, the agency must either issue regulations, consistent with the language and intent of Congress, that permit the dissemination of reference texts or the statute, which permits the dissemination of such texts, will take effect November 21, 1998.

C. The Proposed Regulations Place Unnecessary Limitations on the Waiver of the Requirement to Submit a Supplemental Application for the New Use (Proposed 21 C.F.R. § 99.205)

In order to support the dissemination of important scientific information on off-label uses while at the same time encouraging manufacturers to conduct the studies necessary to permit inclusion of such uses on product labels, Congress decided to require that a manufacturer who seeks to disseminate information about a new use must either certify that it has filed or within six months will file a supplemental

application or submit a proposed protocol and schedule for conducting the necessary studies and a certification that a supplemental application will be filed within 36 months. 21 U.S.C. § 360aaa-3. Recognizing, however, that under certain circumstances it may be appropriate to permit dissemination of information while exempting a manufacturer from filing a supplemental application, section 401 authorizes exceptions to the requirement if the cost of the studies would be economically prohibitive or if conducting the studies would be unethical. As described below, we object to FDA's proposed regulation implementing the statutory exemptions based on costs and ethical considerations because they are inconsistent with the clear language of FDAMA and the intent of Congress.

1. Exemptions Based on Economic Limitations (Proposed 21 C.F.R. §§ 99.205, 99.305)

Section 401 of FDAMA includes a provision authorizing FDA to waive the requirement that a manufacturer ultimately submit a supplemental application on the off-label use described in a journal article if it would be "economically prohibitive" to conduct the studies necessary to support the supplement. 21 U.S.C. § 360aaa-3(d). FDA's proposed regulations provide that in order to demonstrate eligibility for this exemption the manufacturer must show:

> That the estimated cost of the studies needed to support the submission of a supplemental application for the new use exceed the estimated total revenue from the drug or device less the cost of goods sold and marketing and administrative expenses attributable to the product and there are not less expensive ways to obtain the needed information.

Proposed 21 C.F.R. §§ 99.205 (a)(1)(ii) and 99.305 (c)(l)(ii). There are two aspects of this standard that are problematic. First, we are troubled by the requirement that manufacturers demonstrate that the costs of studies needed to support the submission of a supplemental application exceed the total revenue from all *sales* of the product (minus expenses), not just sales for the new use. Requiring that estimates of economic benefit to the manufacturer be equal to the prevalence of all diseases or conditions that the drug will be used to treat is totally at odds with the intent of the provision -- which was to authorize a waiver based on the economics of the *new* use. This intent is demonstrated by examination of the statutory provisions themselves. The two statutory considerations for determining whether studies would be economically prohibitive are (a) the lack of exclusive marketing rights *with respect to the new use* and (b) the size of the population expected to benefit *from approval of the supplemental application.* See *21* U.S.C. § 360aaa-3(d)(2)(A). Thus, we believe that the exemption envisioned by Congress requires FDA to focus solely on the sales from the new use in determining whether the costs of studies necessary to complete a supplemental application would be economically prohibitive.

We also are concerned with the notion expressed in the proposed regulations that in order to convince FDA that an exemption is appropriate, a manufacturer must virtually "open its books" to FDA in order to provide the plethora of commercial information the agency intends to require for its independent review. Proposed 21 C.F.R. § 99.205 (b)(l) (ii)(A). The data FDA has proposed to request is unreasonably broad and amounts to a fishing expedition on the part of the agency for information FDA is not otherwise entitled to see, including market share information and projection and justification of pricing decisions. Not only are we concerned that FDA lacks the expertise to fairly and adequately assess information of this sort, but to the

extent commercial information is provided to the agency, no provision is made to protect the confidential nature of such information. 4/

Finally, we object to FDA's perception that "Congress made it very clear that exemptions from the requirements to submit a supplement are to be rare." See 63 Fed. Reg. at 31149. FDA lacks a statutory basis for this statement. Indeed, the only reference of this sort of which we are aware is the statement by the conferees that exemptions based solely on the size of the patient population are "intended to be the exception, rather than the rule. " H.R. Rep. 105-399 at 15. As we have repeatedly acknowledged, there is no doubt that Congress intended to encourage the conduct of studies in support of supplemental applications. We do not agree, however, that Congress expected the agency to narrow the criteria for the statutory exemption provided by the economically prohibitive provision to the extent it has done so in the proposed regulation.

The statutory provisions applicable to the economically prohibitive provision require an examination of market exclusivity status and estimated population served by the new use. BIO urges that the final regulations should be revised to reflect these criteria. Such a rule will more clearly reflect Congressional intent and require minimal resources to implement.

4/ In response to the agency's request on page 31149 for input regarding use of outside auditors in lieu of submission from the company to FDA, we support providing companies with the option of using an auditor's report as opposed to a submission from the company. It is important to note that this is not the real issue here, however. Regardless of whether the information came from an auditor's report or from a company submission, FDA's regulations inappropriately seek information which is unnecessary to their decision and to which the agency is not entitled.

2. Exemptions Based on Ethical Considerations
(Proposed 21 C.F.R. §§ 99.205, 99.305)

The new law also authorizes FDA to waive the requirement that a company ultimately submit a supplemental application on the off-label use described in the journal article upon a determination that it would be unethical to conduct studies necessary to support the supplement. 21 U.S. C. § 360aaa-3(d). Proposed section 99.205(b)(2) would impose a requirement that the manufacturer demonstrate: (1) why existing data are insufficient to demonstrate safety or effectiveness and (2) why it would be unethical to conduct further studies necessary for approval of the new use. Proposed 21 C.F. R. § 99.205(b)(2). Proposed section 99.205 (b)(2)(ii) would limit application of this exemption to those situations when "withholding the drug in the course of conducting a controlled clinical study would pose an unreasonable risk of harm to human subjects." 63 Fed. Reg. at 31149. The proposed regulation goes on to note that an unreasonable risk of harm ordinarily would arise only when the new use appears to affect mortality or irreversible morbidity.

This is contrary to the statute. The statute clearly provides that manufacturers should not be required to conduct trials in support of a supplemental application where patients would be denied the standard of medical care by taking part in a clinical trial. The statute states that in making determinations regarding exemptions "the Secretary shall consider (in addition to any other considerations the Secretary finds appropriate) whether the new use involved is the standard of medical care for a health condition." 21 U.S.C. § 360aaa-3(d)(2)(B). The Conference Report that accompanies

this legislation makes it clear that where a therapy represents a standard of medical care, investigations of that therapy should be considered for exemptions.

> In making the determination of whether to grant an exemption pursuant to subsection (d)(2), the Secretary may consider, among other factors, whether: the new use meets the requirements of section 186(t)(2)(B) of the Social Security Act; a medical specialty society that is represented in or recognized by the Council of Medical Specialty Societies (or is a subspecialty of such society) or is recognized by the American Osteopathic Association, has found that the new use is consistent with sound medical practice; the new use is described in a recommendation or medical practice guideline of a Federal health agency, including the National Institutes of Health, the Agency for Health Care Policy Research, and the Centers for Disease Control and Prevention of the Department of Health and Human Services; the new use is described in one of three compendia: The U.S. Pharmacopoeia-Drug Information, the American Medical Association Drug Evaluation, or the American Hospital Association Formulary Service Drug Information; the new use involves a combination of products of more than one sponsor of a new drug application, a biological license application, a device premarket notification, or a device premarket approval application; or the patent status of the product.

H.R. Rep. 105-399 at 100.

Further, this proposed regulation fails to take into account the difficulty -- or even impossibility -- of enrolling patients in a study in which some subjects will receive a placebo when a patient can go to a doctor and receive a prescription for the same drug. In BIO's view it is unethical to ask them to do so, when a therapy is known to be effective -- despite the absence of complete data to support a supplement. In fact, to require clinical trials when the treatment being investigated is the standard of care may be contrary to the Declaration of Helsinki of the World Health Organization, which provides that "[i]n any medical study, every patient -- including

those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic methods." 5/ In addition, when patients already have access to a drug that is considered to be effective, patients are unlikely to agree to participate in a study where they may or may not receive the drug. In the experience of our member companies, physicians flatly refuse to participate in placebo-controlled studies of therapies they already believe to be effective. FDA must be mindful of the reality of this situation when finalizing regulations implementing this exception.

To address these concerns, FDA must make several changes to this proposed regulation. First, the agency must delete the limitation that this exemption applies only to new uses that "affect mortality or irreversible morbidity". This limitation runs counter to the language and intent of the statute. Second, FDA should include the language from the House Report, quoted above, and preamble in the regulation that describes the circumstances under which a new use is considered a standard of medical care. Finally, the regulations should clarify that where a new use constitutes a standard of medical care, it would be unethical to conduct clinical trials with that therapy and the agency will grant the manufacturer an exemption from the requirement to file a supplement.

D. FDA's Proposed Regulations Inappropriately Seek to Require Manufacturers to Distribute Additional Information not Required by the Statute (Proposed 21 C.F.R. § 99.103)

The law requires that a manufacturer distribute, along with the information to be disseminated under this section, certain information, including, if applicable, that

5/ Declaration of Helsinki VI, 41st World Medical Assembly, Hong Kong, September 1989, Principle 11.3.

the information is being disseminated at the expense of the manufacturer, the name of any authors who are employees of, consultants to, or have received compensation from the manufacturer, and the official labeling for the drug. 21 U.S.C. § 360aaa(b)(6)(A). The law also provides that the manufacturer must distribute a bibliography of other articles or reference texts that have been previously published about the drug for the use covered by the information disseminated. Id. at § 360aaa(b)(6)(B). Finally, if FDA determines and notifies the manufacturer it has determined that the information proposed for dissemination by the manufacturer is not objective and balanced, it may require that additional objective and scientifically sound information be disseminated, including an objective statement, drafted by FDA, regarding the safety or effectiveness of the new use of the product. Id. As described below, however, several of FDA's proposed regulations designed to implement these provisions of the law are not faithful to the language of the statute but add additional requirements designed to inhibit the free flow of information.

1. "Any Additional Information Required by FDA"
(Proposed 21 C.F.R. § 99.103(a)(4))

Lacking any basis in the law, proposed section 99.103(a)(4) requires that "any additional information required by FDA' be attached to the front of the disseminated materials. Such a requirement could only be written by someone who had no intention of faithfully carrying out the statute. If additional materials, consistent with the statute, are required to be disseminated, they should be presented in a logical manner determined by the manufacturer on a case-by-case basis. The most logical presentation and the one least likely to confuse or mislead readers generally will be to attach FDA-required materials to the back of the materials prepared by the manufacturer for dissemination. A sticker could be prominently placed on the front of

the materials alerting the reader that additional information, included at the request of the agency, is attached to the article or reference text. Such an arrangement would be much more reader-friendly and consistent with the purposes of the statute. Accordingly, we recommend dropping the language "which shall be attached to the front of the disseminated information" from proposed section 99.103(a)(4).

Finally, proposed section 99. 103(a)(4) fails to make it clear that the manufacturer is entitled to receive an opportunity to meet regarding this matter. The law clearly requires the agency to provide an opportunity to meet on the matter prior to FDA requiring the manufacturer to include such information. 21 U.S.C. § 360aaa(c). Proposed section 99.1 03(a)(4) should either reference proposed section 99.301 (a)(3), which does provide manufacturers with the opportunity to meet, or incorporate the same language.

2. Prominence Requirements (Proposed 21 C.F.R. § 99.1 03(b))

The law requires that disclosures be "prominently displayed." 21 U.S.C. § 360aaa(b)(6). Proposed section 99.103(b) appropriately includes language contained in other FDA regulations regarding prominence and how the agency will determine whether a given statement is prominently displayed. However, proposed section 99. 103(b) also includes a requirement that statements be outlined, boxed, highlighted, or otherwise graphically designed to separate that information from the other information being disseminated. This requirement lacks any foundation in the statute which requires only that mandatory disclaimers be "prominently displayed." Manufacturers should retain some discretion to determine how to meet the statutory

requirement. This portion of proposed section 99.103(b) is unnecessary and should be omitted.

3. Disclosure That Use Has Not Been Approved by FDA (Proposed 21 C.F.R. § 99.103(a))

As noted above, the statute requires that the manufacturer disclose that the information concerns a use of a product not approved by FDA. 21 U.S.C. § 360aaa(b)(6). The statute does not, nor should FDA, require specific language to convey this fact. This disclosure, like the others included in section 551(b)(6) of the FD&C Act, only need be appropriately -- namely, clearly and conspicuously -- conveyed by the manufacturer. Instead, the proposed regulations contain required language for this disclosure, proposed 21 C.F.R. § 99.103(a). There is no reason to limit manufacturers' flexibility in this manner. The language proposed or similar language should be offered only as a safe harbor. In other words, the regulation should be revised to provide that if the proposed language is used, the disclosure will meet the requirements of the statute. However, manufacturers should be allowed to propose and FDA to accept alternative language that conveys the same information. The regulations should be amended to make the proposed mandatory language a safe harbor provision.

E. FDA Must Clarify the Relationship Between the Proposed Regulations and the Existing IND Regulations (Proposed 21 C.F.R. § 99.201(a))

The law provides that manufacturers wishing to disseminate information under this section that have not begun clinical trials under an IND must include in their submissions a proposed protocol and schedule for conducting the required studies. 21 U.S.C. § 360aaa-3(c). The proposed implementing regulations would require that the

manufacturer submit such protocols and that they comply with the applicable requirements in part 312 of the regulations. Proposed 21 C.F. R. § 99.201 (a)(4) (ii). Further, the preamble to the proposed rule states that FDA will consider the proposed protocols an original IND or an amendment to an existing IND. 63 Fed. Reg. at 31148. Proposed section 99.301 (b)(l) provides that until FDA notifies the manufacturer that the proposed protocols are adequate and the schedule is reasonable, that the manufacturer may not disseminate information.

We have several concerns regarding the proposed regulations. First, if the protocols submitted to FDA are to be treated as INDs or amendments thereto, under the existing IND regulations the manufacturer may commence such studies within thirty days unless the agency places the study on clinical hold. 21 C.F. R. § 312.40(a). Proposed sections 99.201(a)(2) and 99.301(b)(l) should be revised to be made consistent with the existing IND regulations or, at a minimum, state that nothing in the new regulation is intended to alter the requirements of section 312.40(a).

Second, if the agency does not place a clinical hold on the proposed protocol within the required thirty days, the agency should not then be allowed on day sixty, after the trial has begun, to determine that the proposed protocols are inadequate or the schedule unreasonable. Moreover, even if a protocol is put on clinical hold within thirty days, this should not be dispositive of the decision, required to be made in sixty days, regarding the dissemination of information. Finally, if FDA determines that the protocols are “adequate,” the agency should be bound by this decision and proposed section 99.301 (b)(1) should be amended to reflect this fact.

F. FDA's Proposed Regulations Fail to Require Prompt Review by the Agency (Proposed 21 C.F.R. §§ 99.201(d), 99.301(a))

The law requires that a person wishing to disseminate information under the new law provide the required information to the agency sixty days prior to such dissemination. 21 U.S.C. § 360aaa(b)(4). The statute also provides that FDA must approve or deny an application for an exemption from filing a supplement within sixty days of receipt of such application. Id. at § 360aaa-3(d)(3). FDA's proposed implementing regulations inappropriately seek to enlarge the congressionally-established time frames for review. Proposed section 99.201 (d) provides that the sixty-day period begins "when FDA receives a complete submission. . . . For purposes of this part, a submission shall be considered to be complete if FDA determines that it is sufficiently complete to permit a substantive review. " 21 C.F. R. § 99.201 (d). Proposed section 99.301 (a) provides that within sixty days of receiving a submission, application, or request, the agency may (1) determine that it meets the applicable requirements and the manufacturer may disseminate; (2) request additional information; or (3) determine that the information fails to meet the applicable requirements. Id. at 99.301 (a).

FDA's proposed regulations enlarge the statutorily established time frames of sixty days for review. For example, FDA proposes that the sixty-day time clock will not begin until FDA determines that the submission is sufficiently complete to permit a substantive review, yet does not set a time-certain for the agency review of the submission for completeness. Accordingly, under the regulations the agency has proposed, FDA could wait for two or three months to determine whether the submission is complete, thus starting the sixty day time clock months after the submission was filed. To remedy this, FDA should provide that the agency has a certain number of days to determine whether the submission is complete enough to enable the agency to review

it. In other words, to be consistent with the statute, proposed section 99.201(d) should be revised to provide that the agency has, for example, fifteen days from the date of receipt of a submission to determine whether it is sufficiently complete to be reviewed. If it is, the agency must act on the submission within sixty days of the date the submission was received. This procedure is consistent with the way in which FDA manages its time commitments to review applications submitted under the Prescription Drug User Fee Act.

The agency should revise proposed section 99.301 (a) in a similar manner to provide for review consistent with the statutory time frames. For example, the statute requires that FDA approve or deny an application for an exemption within sixty days. Currently, the proposed regulations allow the agency to approve, deny or request additional information within sixty days. As addressed above, FDA inappropriately is seeking to extend the review times established by Congress. Further, the proposed regulations do not appear to require the agency to notify the sponsor why the submission is inadequate and more information is needed. Accordingly, proposed section 99,301 (a) should be revised to require that FDA make an initial determination within fifteen days after an application, submission or request is filed with FDA regarding whether more information is required. If such information is required, in this initial time frame, the sponsor should be notified why the submission is inadequate and the additional information is needed. The agency should then be required to approve or deny a submission within the sixty days provided by Congress. It is worth noting that this enlargement of the Congressionally-established time frames for review would be unnecessary if the regulations applied the statute as written instead of second-guessing

the peer-review process and allowing FDA to do its own scientific analysis of the materials intended for dissemination. 6/

G. FDA's Attempt To Preview Clinical Data is Inappropriate
(Proposed 21 C.F.R. § 99.301(b)(2))

The law provides that sixty days prior to dissemination, a manufacturer supply FDA with any clinical trial information the manufacturer has relating to the safety or effectiveness of the new use. 21 U.S.C. § 360aaa(b)(4). Proposed section 99.301 (b)(2) would allow FDA to "conduct a preliminary review of the completed study reports to determine whether they are potentially adequate to support the filing of a supplemental application for the new use, " 21 C.F.R. § 99.301(b)(2). This requirement lacks adequate foundation in the statute.

The agency is not entitled to a "sneak peek" at preliminary clinical trial data prior to its submission to the agency in the form of a supplemental application. Such a previewing of the data may cause the agency to prejudge the supplemental application before the manufacturer even submits it to the agency. This type of inquiry simply is not authorized by the statute. Accordingly, proposed section 99.301(b)(2) should be deleted.

6/ Likewise, the regulatory program the agency has proposed is very resource-intensive. If the agency implemented the program as written, where the agency simply determined whether the article met the statutory standards and did not second-guess the peer-review process, the program would not be nearly as costly to the agency.

H. FDA's Proposed Recordkeeping and Reporting Requirements Are Ambiguous and Unnecessarily Burdensome (Proposed 21 C.F.R. § 99.501)

As described below, section 99.501 of the proposed regulations would impose burdensome recordkeeping and reporting requirements on manufacturers.

1. Recordkeeping and Reporting Requirements Tracking Individual Recipients versus Categories (Proposed 21 C.F.R. § 99.501(a))

Proposed section 99.50 1(a) would require that manufacturers maintain records identifying, either by name or by category, those person to whom they have disseminated information on a new use. The proposed regulations would permit FDA to require that a manufacturer maintain records by name. Proposed 21 C.F. R. § 99.501(a). In the preamble, however, the agency has stated that in most cases it does not intend to do so. While these requirements track the statute, the agency piles on additional requirements. Id. at § 99.501 (a)(I) (ii)(A). These additional requirements should be deleted from the final regulations.

Our concern is that, if the agency does not require a manufacturer to maintain records identifying recipients of disseminated information by name, if corrective action later is required, manufacturers should not be subject to enforcement action for not possessing such lists. In other words, if the agency requires a manufacturer to maintain records identifying recipients of disseminated information by category -- which we believe is appropriate -- should corrective action later be required, corrective action designed to reach those categories should satisfy the manufacturer's obligation. FDA cannot expect manufacturers to generate such individually targeted lists for corrective action ex *post facto*. The current language of the preamble and

regulation are ambiguous on this point and FDA should clarify this by regulation. Manufacturers are entitled to such certainty.

2. Reporting Requirements on Ongoing Trials (Proposed 21 C.F.R. § 99.501(b))

Proposed sections 99.501 (b)(3) and (b)(4) would require manufacturers to submit semi-annual reports containing, among other things, summaries of any additional clinical research or other data relating to the safety or effectiveness of the new use, including copies of any clinical research possessed by the manufacturer. Proposed 21 C.F.R. § 99.501(b)(3). In addition, manufacturers conducting studies necessary for the submission of a supplemental application are required to provide updates on such studies and, if discontinued, the reason for the discontinuance. Id. at § 99.501(b)(4).

These reporting requirements are duplicative of existing Investigational New Drug ("lND") reporting requirements. Because manufacturers already would be required to submit similar reports under the IND regulations, the proposed regulations are unnecessarily burdensome. Accordingly, FDA should either delete these proposed regulations or, at a minimum, harmonize them with existing IND requirements, including requirements relating to content and timing.

3. Reports on the Continued Need for the Exemption (Proposed 21 C.F.R. § 99.501 (b)(5))

Proposed section 99.501 (b)(5) requires that a manufacturer granted an exemption from the requirement to submit a supplemental application must submit to FDA, on a semi-annual basis, "any new or additional information that relates to whether the manufacturer continues to meet the requirements for such exemption." 21 C.F. R.

§ 99.501(b)(5). The regulation goes on to state that this information would include any information regarding revenues from sales of the product or new or additional information regarding the persuasiveness of the data. Id. This proposed regulation would require that manufacturers produce extensive market data. The cost of generating the required information is economically prohibitive. Given the economic burden it would impose, such a requirement is unacceptable to industry and should be deleted.

4. Corrective Actions
(Proposed 21 C.F.R. § 99.401)

As part of section 555, Corrective Actions; Cessation of Dissemination, Congress imposed obligations on manufacturers to supply additional information to FDA after dissemination of an article commences as follows:

> After a manufacturer disseminates information under section 551, the manufacturer shall submit to the Secretary a notification of any additional knowledge of the manufacturer on clinical research or other data that relate to the safety or effectiveness of the new use involved. If the manufacturer is in possession of the data, the notification shall include the data. The Secretary shall by regulation establish the scope of the responsibilities of manufacturers under this paragraph, including such limits on the responsibilities as the Secretary determines to be appropriate.

21 U.S.C. § 360aaa-4(a)(2) (emphasis added). Obviously, Congress concluded that it was important that FDA set forth, by regulation, the "limits on the responsibilities" of manufacturers "as the Secretary determines to be appropriate." FDA has not issued any proposed regulations on this issue and it must do so.

IV. Conclusion

Clearly, FDA's proposed regulations were drafted by persons who do not respect the Congressional position that dissemination of balanced information on off-label use is appropriate. It denigrates the function of peer review and substitutes FDA's judgment for that of scientific experts in determining whether a study is scientifically sound. It inappropriately limits the types of studies that may be described in journals eligible for dissemination, and imposes requirements for a journal's description of studies that are not met by peer-reviewed scientific journals today. And it makes a mockery of the "economically prohibitive" exception to the requirement to submit a supplement. In many other ways, it piles on new requirements designed to discourage dissemination of peer-reviewed journals and reference texts. The proposed regulations thus totally upset the balance crafted by Congress between the desirability of dissemination of information and the incentives to file a supplemental application.

Sincerely,

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